With respect to (1), the Examiner believes this would be an obvious modification of Suzuki in view of Lenk. More particularly, the Examiner points out that Lenk discloses a method for the size separation of particles by cross-flow filtration which is better than traditional filtration process because it prevents filter cake build-up in the filter surface, eliminates dead-end extrusion of larger particles, and allows for the maintenance of the flow rate of the liquid as it is passed over the membrane (abstract; col. 1, lines 24-46). Lenk discloses that cross-flow filtration is useful in the separation and classification of emulsions according to size (col. 7, lines 31-34). Additionally, Lenk recognizes that cross-flow filtration can be done aseptically, and that the process can be used to remove unentrapped bioactive agent (col. 7, lines 35-38; col. 8, lines 14-15).

In the Examiner's opinion, therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the cross-flow filter of Lenk in place of the filter (e') in Suzuki in order to size the emulsion, prevent filter cake build-up, eliminate dead-end extrusion of larger particles, and remove unentrapped bioactive agent. Specifically, it is noted that it would have been obvious to recycle the unentrapped bioactive agent and utilize it in the formation of the emulsion. The motivation to recycle the unentrapped bioactive agent in the aqueous phase is to prevent adherence of the medicament to the outside of the formed microspheres. Wherein it is undesirable to have the medicament adhered to the outside of the microspheres as recognized by Suzuki [0144].

In continuing to make this rejection, it is believed the Examiner has overlooked the significance of the differences between the invention and Suzuki and the advantages resulting from such differences.

One of the beneficial results enjoyed by the present invention is the drastic downsizing of the apparatus used to prepare the microspheres by recycling the filtrate from the cross-flow filter and using it in the emulsifying step to prepare another emulsion. This is not just a downsizing of the Suzuki apparatus, but a modification in the process that allows such downsizing to occur.

As previously explained, according to the method of the present invention for preparing microspheres (MS), after a part of the emulsion is taken out of the microsphere storage tank and passed to the cross-flow filter, the filtrate thus separated is repeatedly used as an aqueous solution for preparing another emulsion. This is not at all suggested in Suzuki even if, as argued by the Examiner, a cross-flow filter was substituted for the filter e' of Suzuki and even if the filtrate from it is an aqueous solution containing unentrapped bioactive agent that is recycled. The difference is that in Suzuki, the filtrate, whether it contains unentrapped bioactive agent or not, is merely returned to the MS tank, whereas in the invention the filtrate is recycled back to the emulsification step (a) and repeatedly used to prepare yet another emulsion, which is then transferred to the MS tank in step (b). Note in step (d-1)-ii) of claim 1 that the filtrate is not only recycled as an aqueous solution for step (a), i.e., the emulsifying step, but steps (a) to (d-1) are repeated, while evaporating off water-immiscible organic solvent with a hollow fiber membrane module located in the microstorage tank, to accumulate microspheres in the tank until the required amount of microspheres are produced which are then collected in step (e) after step (d-1) is completed. See also page 24, line 16 to page 25, line 13 of the specification which further describes this feature of the invention. It is important to note that in the invention the filtrate is recycled

to the emulsification step, not to the MS vessel as in Suzuki. No such step is taught or even remotely suggested in Suzuki.

In the preparation of MS, for example, by the method of Suzuki Example 5, the starting material for MS, the medicament (vitamin B_{12}) and a polymer (polylactic acid-glycolic acid copolymer) (totally 2 g) and organic solvent (3 g) were used and an aqueous solution (500 ml or more) was required. Thus, in this method, a large amount of water is required for preparing MS even in a small amount, for which a large apparatus is necessary for preparing such a small amount of MS. In such a method, even if the MS could be obtained in a yield as high as 100%, in order to produce 100 kg of MS, an aqueous solution of 25,000 L (about 25 tons) or more is required. Hence, an apparatus for containing such a large amount of materials is required.

On the contrary, according to the method of the present invention, the amounts of water as shown in the following Table 1 are sufficient for obtaining MS (100 kg) for each noted cycle times.

Table 1

Cycle times*	Amount of aqueous solution
10 times	2500 L
20 times	1250 L
50 times	500 L
100 times	250L
Suzuki	25000 L

* When the filtrate in the same amount of the aqueous solution for preparing an emulsion within the MS storage tank is used for preparing the emulsion and the emulsion is transferred into the MS storage tank, it is counted as one cycle.

Thus, according to the method of the present invention, the amount of the aqueous solution (which occupies the most space in an apparatus for preparing MS) can be very much reduced and thus the apparatus can drastically be downsized.

According to the known method of Suzuki, a building would specifically need to be built for such an apparatus for preparing MS. On the contrary, according to the present invention, the apparatus can be downsized to the point where it can be set up within a room of an existing building.

Moreover, by downsizing the apparatus, in the case of preparing an emulsion for a medicament under aseptic conditions, the method of the present invention avoids the production of unfavorable inhomogeneous emulsions. In the case of producing MS on an industrial scale using a large apparatus, there are usually problems of nonuniformity of the product (e.g., inhomogeneous emulsification, nonuniform temperature of emulsion and biased organic phase in the emulsion). However, according to the present invention, such unfavorable uniformity can be avoided and the desired MS can be obtained very easily and with high quality. In large scale methods, the large amount of water needs to be wholly sterilized, but in the method of the present invention, the aqueous solution sterilized in the first cycle can be maintained under aseptic conditions in the subsequent cycles. Hence, it is much easier to maintain aseptic conditions in the method of the present invention.

Thus the method of preparing MS of the present invention is based on the novel idea of recycling the aqueous solution as the filtrate of a cross-flow filtration step for

preparing further emulsions, by which the apparatus can be significantly downsized. In contrast, in Suzuki whether the filter is a cross-flow filter or not, any "aqueous solution" is returned to the MS vessel and it is not used to prepare another emulsion as claimed.

Another advantage of the present invention is that by merely changing the circulation times, various amounts of MS can easily be produced. For example, as shown in Table 2 below when the amount of aqueous solution is 250 L, the amount of MS produced can be controlled by the number of cycle times.

Table 2

Cycle times	Amount of MS
100 times	100 Kg
50 times	50 Kg
20 times	20 Kg L
10 times	10 Kg
Known method	1 Kg

Thus, according to the method for preparing MS of the present invention, one apparatus may be used in various scales of MS production, and once it is controlled in an antiseptic condition, the antiseptic condition can easily be maintained. On the other hand, according to the known method as explained by Suzuki, the apparatus would be repeatedly used and need to be sterilized each time, which are disadvantageous in the production of the desired MS efficiently as well as in the costs therefor.

With respect to (2), as has been previously explained, the steps of (i) filtration with a cross-flow filter, (ii) emulsification with an emulsification device and (iii) evaporation of the organic solvent by passing the emulsion through a hollow fiber

membrane module in the MS storage tank can be done in parallel. Hence, the organic solvent can rapidly be removed from the produced emulsion and the formation of MS is promoted and thereby clogging of the cross-flow filter can be inhibited. Hence, the method of preparing MS of the present invention can be done with much higher efficiency in comparison with conventional methods.

The Examiner repeatedly argues that it would be obvious to combine the location of the hollow fiber membrane module in the MS storage tank and to use cross-flow filtration in view of the disclosure of a hollow fiber membrane module in the MS storage tank in Suzuki and the disclosure of use of a cross-flow filter in Lenk, but this is without any explanation of which situation in Suzuki the hollow fiber membrane module is located in the MS storage tank.

More particularly, the Examiner is arguing that it would be obvious to use the filter of Lenk in the circulation method of Suzuki as shown in Fig. 1 thereof, but here the hollow fiber membrane is used outside of the MS storage tank. On the other hand, while the hollow fiber membrane is located inside the MS storage tank in the immersing method of Suzuki as shown in Fig. 2 thereof, here there is no filter of any sort used. Thus it is submitted the Examiner has improperly combined the teachings of Suzuki to try and arrive at Applicants' invention without adequately explaining how, if a cross-flow filter was used in Fig. 1 in view of Lenk for filter e', the hollow fiber membrane could be located in the tank of Fig. 1 and the apparatus still produce MS. That is because any teaching of how to do so comes from a reading of Applicants' specification and not from any thing taught by Suzuki.

In summary, according to the method of the present invention for preparing MS, after the step of taking out a part of the emulsion from the MS storage tank and filtering

it in a cross-flow filer, the filtrate from the filtration is repeatedly used as an aqueous solution for preparing another emulsion. It is because of this in combination with the hollow fiber membrane being located in the storage tank for removal of the organic solvent, that the apparatus can be significantly downsized while still producing significant quantities of MS. There simply is no teaching whatsoever to reuse filtrate as an aqueous solution for preparing further emulsions taught in either of the cited references, regardless of how the apparatuses of Figs. 1 and 2 are combined with Lenk or with each other.

Reconsideration of the rejection of claim 1 and the claims dependent therefrom for being obvious over Suzuki in view of Lenk and their allowance is therefore requested.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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